REVIEW

Antibiotic resistance: location, location, location

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ABSTRACT

Antibiotic resistance surveys are published widely, citing percentage resistance rates, sometimes for vast transcontinental regions. Such data seem straightforward, but when one drills deeper, great complexity emerges. Rates for methicillin resistance among *Staphylococcus aureus* from bacteraemias vary from <1% to 50% among European countries, and vary greatly among both hospitals and hospital units. Methicillin-resistant *S. aureus* (MRSA) resistance rates are typically higher for tertiary-care hospitals and intensive care units than in general hospitals and wards, and lowest in single specialist centres. The likelihood of resistance also varies according to patient characteristics: those patients from nursing homes and with underlying disease, recent antibiotic treatment and hospitalisation are more likely to harbour resistant pathogens. Percentage rates themselves also may be misleading; they may be high only because the denominator is small or inaccurate; i.e., resistance may be common but the pathogen rare. Measures of disease burden—cases per 1000 bed-days or per 10^5 individuals—overcome this deficiency but are harder to collect, influenced by case mix, and associated with other problems: how to count part days or infections acquired elsewhere; most important, are all cases captured? National or international resistance statistics may illustrate trends and provide benchmarks, but for patient management, good local data are essential. Which units are most affected? Are the resistant infections locally acquired or imported with transferred patients? Are the resistant isolates clonal, indicating cross-infection, or diverse, indicating repeated selection or reflecting antibiotic policy? Unless these aspects of infection are considered, interventions to reduce resistance may be misdirected.

Keywords Antibiotic resistance, epidemiology, resistance surveillance

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INTRODUCTION

Antibiotic resistance varies with time and place. On the 'macro' level, it varies among countries, with occasional paradigm shifts as new resistance types proliferate. At the 'micro' level, antibiotic resistance varies among units within a hospital and among patient groups. This article seeks to illustrate these differences, highlighting the need for good local surveillance as well as for broad national data. The national data show secular trends, while local data underpin antibiotic policies, infection control, and empirical antibiotic choices. We aim also to highlight the cautions necessary when reading and interpreting resistance surveys. We do not seek to criticise these surveys, for they remain the best source of data available, and 'perfect' surveillance is prohibitively expensive; rather, we try to help the reader navigate around the potholes.

It should be noted, first of all, that practically all surveillance of resistance considers only those isolates *routinely* submitted to microbiology laboratories. Bacterial culture and susceptibility testing is generally undertaken for severe infections in

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hospitals; for community infections, however, it is biased towards complex cases, potentially overestimating the extent of resistance [1]. Around 50% of community urinary infections receive microbiological investigation in the UK; however, for respiratory infections [2], the rate falls to 3%. Moreover, individual general practitioners vary greatly in their propensity to submit specimens for culture and susceptibility testing. For urine cultures, the UK submission rate ranges from 29 to 296 samples per 1000 registered patients per annum [3], and many practitioners submit samples only from those patients who are responding poorly to empirical treatment—perhaps because their infection was caused by a resistant strain. Evidently, these form a biased sample.

Insight into the extent of this distortion is provided by a recent study of uncomplicated cystitis in Norwich and Gloucester (UK), which sampled consecutive patients on the basis of clinical symptoms and found a trimethoprim resistance rate of 13.9%, compared with rates of 24–27% among urinary isolates routinely submitted to the two laboratories [4]. More notoriously, penicillin-resistant pneumococci are well-represented in many resistance surveys but prove remarkably scarce when consecutive patients in the same regions are recruited for prospective antibiotic trials. It is not clear whether this is because the surveys overestimate resistance, owing to sample bias, or because the trials mostly exclude those complex, frequently treated patients who are most likely to harbour resistant bacteria. All resistance surveys, but particularly those of community pathogens, should be read with these caveats in mind.

VARIATION BY COUNTRY

Several large international programmes undertake surveillance of resistance, or have done so until recently. These include SENTRY [5], PROTEKT [6], SMART [7], MYSTIC [8], and the Alexander Programme (http://www.alexandernetwork.com), all with high-quality microbiological data. Their results illustrate gross trends, but the programmes have only a handful of collecting sites per country, and these are often major teaching or tertiary-care centres, potentially creating sample bias, since these hospitals tend to manage the most complex patients (see below). The number of isolates sampled per annum is fewer than 10 000 in all of these surveys and, as with political opinion polls, it is remarkable that the results often agree so well, or show so little year-to-year fluctuation!

What is more, surveys often present results for huge geographical regions, e.g., Europe or the Western Pacific (meaning East Asia, Australia and Oceania), which include a great diversity of countries and peoples, varying greatly in how their medical systems are organised, in their control of public access to antibiotics, and in the emphasis they may give to hospital infection control. Major differences emerge if one drills deeper, using surveys that consider only single regions, and with numerous collection sites (e.g., http://www.earss.rivm.nl or http://www.bsac-surv.org). As is well-known, the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates from patients with bacteraemia is much lower in Scandinavia and The Netherlands than elsewhere in Europe [9] (Table 1). Other examples are that MRSA is less prevalent in Canada than the USA [10], and that, within the Western Pacific region of, for example, the SMART programme, numerous resistances among Gram-negative bacteria are less prevalent in New Zealand and Australia than in China or Southeast Asia [11].

The high MRSA rates in southern Europe, the UK and Ireland are relatively stable, having persisted at 30–40% for at least 5 years, whereas the now-high rates in much of central Europe have been rising steeply in the same period (http://www.earss.rivm.nl). The low Scandinavian and Dutch rates reflect extremely stringent 'search and destroy' infection control policies which quarantine high-risk hospital admissions (e.g., those from other countries or with suspected MRSA contact) until they have been proven not to be carriers. When MRSA infections do occur, the Dutch and Scandinavians put emphasis on eradication from any contacts who may have become colonised or infected [12]. Where necessary, contaminated wards are closed and deep-cleaned. Such policies work, although they may be practicable only when MRSA rates are low. Elsewhere in Europe (and in most of the rest of the world), MRSA rates have crept above some still undefined threshold where, given bed-pressure, 'search and destroy' has become impracticable [13]. The alternatives adopted—pre-admission screening for elective admissions, surveillance cultures, continual re-emphasis of hand hygiene,

Table 1. Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia rates across Europe, based on EARSS data for 2004 [22]

Country	MRSA as % *S. aureus*	MRSA bacteraemias per 10^5 bed days
Iceland	0	<0.96
Norway	<1	0.12
Sweden	<1	0.26
Denmark	1	No data
Netherlands	1	0.35
Finland	3	0.8
Estonia	5	0.34
Czech Republic	9	1.02
Slovenia	12	2.04
Austria	14	No data
Luxembourg	16	No data
Hungary	17	1.27
Germany	19	3.29
Slovakia	19	2.00
Poland	20	1.12
Bulgaria	24	1.53
Latvia	25	1.72
Spain	26	6.00
France	29	11.79
Belgium	33	7.75
Croatia	38	6.14
Israel	39	12.16
Italy	40	6.44
Ireland	41	12.02
Greece	44	7.36
UK	44	9.56
Portugal	46	17.58
Cyprus	49	7.91
Malta	56	19.29
Romania	73	1.92

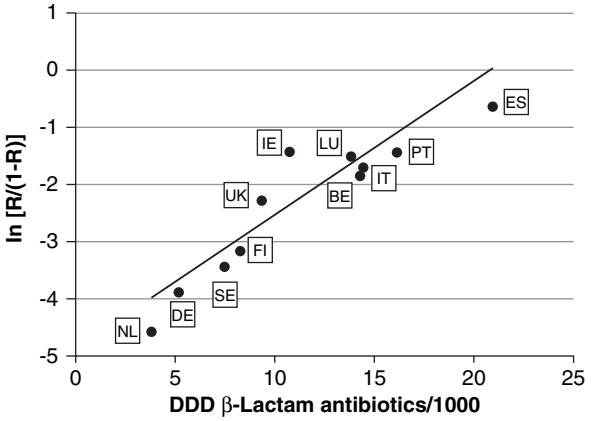

Fig. 1. Relationship between community penicillin usage in defined daily doses and penicillin resistance (expressed as the natural logarithm of the probability of resistance in any given isolate) among pneumococci from bacteraemia in different European countries, 2005; reproduced from Bronzwaer *et al*. [15] with permission. Codes are: NL, The Netherlands; DK, Denmark; SW, Sweden; FI, Finland; UK, United Kingdom; LU, Luxembourg; IE, Ireland; BE, Belgium; IT, Italy; PT, Portugal; ES, Spain.

contact precautions, and use of side rooms or separate wards to isolate and cohort infected or colonised patients—have proved far less effective than the stringent Dutch and Scandinavian methods, although it is debatable to what extent the failures reflect inadequacy of the procedures or their not having being enforced with sufficient single-mindedness in a world of competing priorities and targets [14].

In the case of pneumococci from bacteraemias, there is a remarkable linearity across Europe between the density of outpatient prescribing of penicillins and the prevalence of resistance [15] (figure 1), both of which are higher in the south than in the north [16] or, more precisely- for the rates in Ireland and Poland are high too- in traditionally Catholic Europe than in Protestant. This geographic split is counter-intuitive, for one would expect less prescribing in the south-with its warmer, drier climate, less conducive to respiratory illness. Is the cultural heritage of the Reformation, which redefined relationships between individuals and higher authority, somehow still reflected, in a largely secular age, in cultural propensity to seek medical intervention for respiratory infections? These may seem wild and provocative speculations, but were the conclusions of one study, comparing Middleburg in the Netherlands (historically largely Protestant) with Bruges, 60 km away in Belgian Flanders (speaking the same language but Catholic) [17] (Table 1). Whether one accepts the relationship to cultural background or not (and we advocate caution, for the samples are small), upper respiratory tract infections were largely termed ''colds'' or ''flu'' by the Dutch, who nursed themselves, but ''bronchitis'' by the Belgians, who sought medical attention and received antibiotics (Table 2).

INTERPRETING PERCENTAGE RESISTANCE RATES FROM SURVEYS

It should be added that the percentage resistance rates, as routinely published for surveys and widely cited, potentially give a distorted picture. A rate may be high while the incidence of infection is low. Some of the highest percentage rates published are for resistance in *Enterococcus faecium* and *Acinetobacter baumannii*, but infections

Table 2. Attitudes to antibiotics in Middleburg and Bruges [17]

Survey sites	Bruges, Belgium	Middleburg, The Netherlands
Language	Flemish	Flemish
Nature of town	Prosperous, non-industrial	Prosperous, non-industrial
Cultural background	Catholic	Protestant
Survey participants		
Total interviewed	15	15
Representing family members (*n*)	36	33
Cases of upper respiratory tract infection reviewed	28	20
Patient's description		
'Cold'	4	9
'Bronchitis'	9	–
'Flu'	–	5
'Cough, runny nose'	8	2
'Sinusitis, angina'	7	4
Patient's action		
Consulted doctor	14 (50%)	4 (20%)
Received antibiotics	11 (40%)	3 (15%)
Self-medicated	9	3
'Nursing one's illness'	5	13

with these pathogens are 10- to 100-fold less frequent than those with *S. aureus* and *Escherichia coli* [18]. Multiresistance in *E. coli* and *S. aureus* is therefore the greater concern, and assertions that '*Acinetobacter* is the new MRSA' are exaggerated [19].

Epidemiologists justifiably argue that it is better to cite rates of resistant infection per 10^5 individuals or per 1000 patient-days rather than to quote percentages of resistant isolates, but the former parameters are more difficult to capture and are meaningful only if all cases of infection are recorded. This is unlikely to be true unless reporting is mandatory, as with bacteraemias due to MRSA and vancomycin-resistant enterococci in England [20]. Even then, the resulting rates are distorted by the issue of how to count part-days, which become a greater factor as hospital stays become shorter. Moreover, although an infection may manifest in a hospital, it does not mean that it was contracted there. This is critical for the mandatory MRSA bacteraemia surveillance in the UK, where the rates are the basis for defining MRSA reduction targets for each hospital, but where 8% of MRSA bacteraemias are apparent at the time of hospital admission and a further 25% are manifest within 48 h of admission, implying that the infection originated elsewhere [21].

The EARSS report for 2004 [22] provides data on MRSA bacteraemias per 1000 bed-days across Europe. These incidence rates are much lower for many east European countries than for west European countries with comparable percentage prevalence rates (Table 1). It seems likely that the explanation is simply that blood cultures are done less often in eastern Europe than in the west, especially if the primary focus of the infection is believed to lie elsewhere.

RATES OF RESISTANCE VS. UNIT AND PATIENT TYPE

Within countries, there is great variation in infection and resistance rates among different hospital and patient types. The UK mandatory surveillance for MRSA indicates a higher incidence in teaching hospitals than in large acute-care general hospitals, which, in turn, have higher rates than small acute-care hospitals; the lowest rates are for single-specialty trusts, e.g., those specialising in ophthalmology or orthopaedic surgery (Table 3). A similar relationship between hospital size and MRSA prevalence rate exists in the USA, where the National Nosocomial Infections Surveillance (NNIS), with approximately 300 participating sites, reported that the intensive care units (ICUs) of major teaching hospitals had significantly higher rates of infection than the ICUs of all other reporting hospitals. This may be because they handle more complex and vulnerable patients, with longer lengths of stay and greater exposure to known risk-factors for resist-

Table 3. Incidence rates for methicillin-resistant *Staphylococcus aureus* bacteraemias in England by hospital type [21]

	Cases per 10 000 bed-days	
	April–September 2001	October 2005 to March 2006
Acute teaching	2.38	1.99
Large acute	1.67	1.85
Medium acute	1.42	1.46
Small acute	1.27	1.54
Acute specialist, children	0.83	0.97
Acute specialist	0.74	0.62

ant infections, such as devices, lines and antibiotic treatment [23]. Moreover, the uptrend in MRSA infections through the 1980s and 1990s in the USA was slower and came later in the smaller hospitals [14].

Even discounting such factors, there is still variation in MRSA bacteraemia rates when ostensibly similar acute-care general hospitals in England are compared with each other. Such variation must partly reflect relative attention to infection control and antibiotic usage patterns [24], although the roles of quinolones and cephalosporins in MRSA selection remain controversial [25,26], and a recent study found little correlation between visual cleanliness and the incidence of MRSA bacteraemias [27]. The other critical factor is case-mix: MRSA bacteraemias are rare among maternity and psychiatric patients and in infants, so that large units handling these patients will 'dilute' a hospital's rate, calculated as cases per 1000 bed-days across the whole site [21].

Resistance rates vary *within* hospitals too. The USA's NNIS system showed that resistance rates for many pathogens were highest in isolates from ICUs, lower in other inpatient groups, and lower still among outpatient isolates [23].

Other US and European studies have also identified ICUs as having a higher prevalence of resistant organisms [28] than other hospital areas, while mandatory surveillance reveals that a disproportionately large number of MRSA bacteraemias in England occur in intensive care or nephrology patients [21] (Figure 2).

Other patient groups in which multiresistant organisms are disproportionately prevalent include those who receive multiple rounds of treatment for intractable infections, e.g., cystic fibrosis patients with *Pseudomonas aeruginosa* infection [29]. The rates of resistance in these patients are three to four times higher than among the generality of *P. aeruginosa* isolates, and the isolates are more often hyper-mutable, indicating an increased potential to develop further resistances [30].

E. coli presents another example of the relationship between resistance and patient type. Rates of trimethoprim resistance are significantly

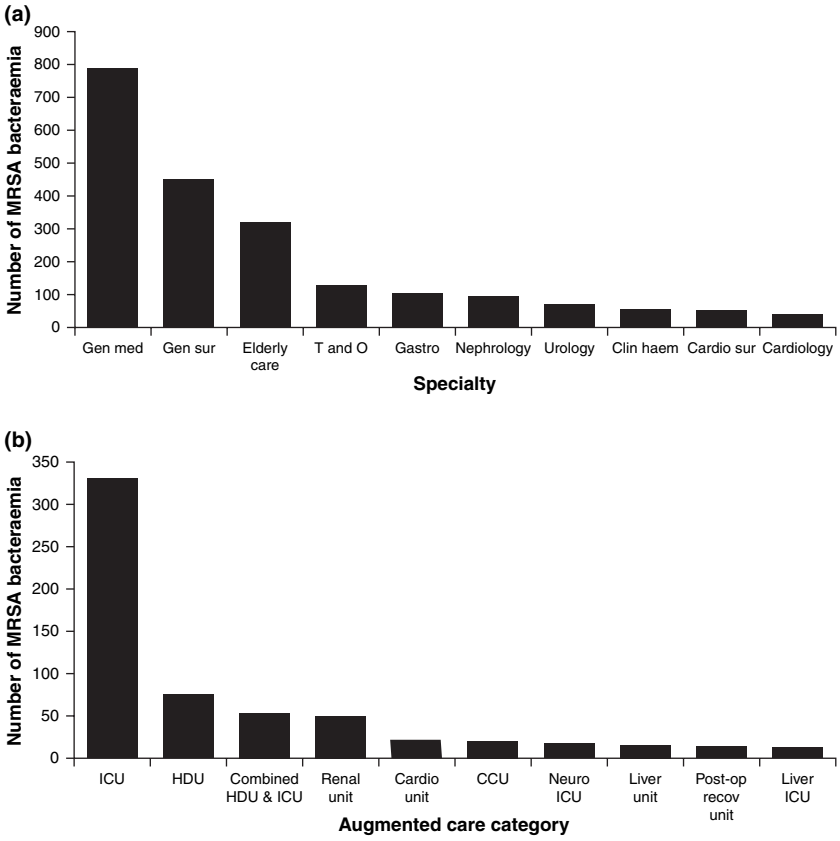

Fig. 2. Numbers of MRSA bacteraemias, detected ≥48 h after admission, in English hospitals in relation to (a) specialty and (b) augmented care category. Codes are: Gen med, general medicine; Gen sur, general surgery; T & O, trauma and orthopaedics; Clin haem, clinical haematology; Cardio sur, cardiothoracic surgery; ICU, intensive care unit; HDU, high-dependency unit; Gastro, Gastrointestinal; Cardio, cardiothoracic; CCU, critical care unit; Neuro ICU, Neurosurgical Intensive Care Unit; Post-op recov, post-operative recovery unit. Data are from [21], reproduced with permission.

increased among isolates from those cystitis patients who have had multiple (≥4) courses of trimethoprim in the preceding months [4,31], while strains with quinolone resistance and extended-spectrum β-lactamases are mostly found in older patients with underlying disease, recent antibiotic treatment, and a history of hospitalisation [32,33]. By contrast, trimethoprim resistance rates among isolates from uncomplicated cystitis patients are lower than those among the generality of isolates submitted to laboratories for culture and susceptibility testing [4].

All these associations carry the implication that the global resistance rates for a species, or even for a species in a particular clinical setting, tell us rather little about the risk of resistance in a particular patient for whom empirical therapy must be selected. Rather, the choice of empirical treatment must also reflect the patient's risk-factors, and this demands not only a radical improvement in the design and understanding of local surveillance, but also better liaison between the laboratory and the responsible clinicians than is often the case at present.

OF STRAIN AND PLACE

Those resistances that evolve by easy mutation, e.g., derepression of the chromosomal AmpC β-lactamase in *Enterobacter* spp., are liable to be selected repeatedly wherever selective pressure by third-generation cephalosporins is exerted [34,35]. Likewise, extended-spectrum mutants of TEM and SHV β-lactamases could evolve on many occasions and at many places, since their parent enzyme types were widespread when the selective third-generation cephalosporins were introduced [36].

By contrast, those resistances that evolve only rarely and do not transfer readily—e.g., methicillin resistance in *S. aureus* or penicillin resistance in pneumococci—disseminate by transfer of strains among people, hospitals and countries. The absence of such a resistance from a particular locale may simply signify that potent, fit strains with the corresponding mechanism have not yet reached that location.

Within countries, resistant clones may remain more or less confined, perhaps reflecting patterns of hospital transfers. In London in the 1980s, the MRSA problem, then due to EMRSA-1, affected hospitals north of the River Thames, only gradually spreading south [37]. The now dominant EMRSA-15 and EMRSA-16 strains emerged and spread in the UK Midlands and south-east [38,39], only gradually moving into northern England and into Scotland. Even now, infections with these (or any other MRSA strains) are very uncommon in hospitals on the Hebrides and Orkney Isles (Eastaway, Health Protection Scotland, personal communication). As a second example, the UK currently has two prevalent *A. baumannii* strains that are resistant to carbapenems: OXA-23 clone 1, and the SE (south-east) clone. Each has been recovered at approximately 40 hospitals serving overlapping patient populations, mostly in London and south-eastern England [40]; neither has yet spread to the Midlands or the North, even 3–6 years after they were first recorded. Carbapenem-resistant isolates from more northerly cities are few in number and are either clonally diverse or, if clonal, localised to a few sites. Of the two major clones, the OXA-23 clone is very susceptible to tigecycline, at least *in vitro*, with MICs ≤0.25–0.5 mg/L, as compared to 1–2 mg/L for the SE clone [40]; the clinical significance of this observation remains to be confirmed. In contrast, a carbapenem-resistant *Acinetobacter* clone with the OXA-40 enzyme is spreading in hospitals around Chicago and is resistant also to tigecycline, with MICs mostly of 4–8 mg/L [41]. It follows that one's optimism about tigecycline as an answer to 'pan-resistant' *Acinetobacter* is likely to be a function of strain and location. It is currently striking; too, that MRSA and extended-spectrum β-lactamases (ESBLs) are evolving differently in the USA and Europe. In Europe, MRSA remains largely a nosocomial problem, with the prevalent strains spreading via the hands of hospital personnel [42]. Most infections occur in elderly patients with underlying disease or those who become contaminated as a result of surgery. Colonisation, but rarely infection, may spread within nursing homes [43]; community-acquired infections remain rare, although there is concern about the community-adapted ST80 lineage [44]. In the USA, by contrast, the increasing problem is with community-acquired MRSA [45]. The newly emerged ST8/USA300 and USA400 lineages responsible for these infections are spread, in markedly younger age groups, by close physical contact, as in sports, gay

bathhouses, and prisons, and as a result of sharing towels and other personal items [46,47].

ESBLs provide the mirror image of this epidemiology: the problem in Europe is increasingly one of *E. coli* with CTX-M-type enzymes, often causing infections that manifest in the community or in nursing homes [48]. The pattern in the USA remains one where most ESBLs are mutants of the old TEM and SHV penicillinases, most often produced by *Klebsiella* spp., just as was previously the case in Europe. These differences are likely to erode as the more successful strains become globalised. There are already reports of the American community MRSA strain USA300 in Europe [49] whilst *E. coli* strains with CTX-M-15 β-lactamase have been reported to be disseminating in Canada [50].

Even when different locales have epidemiologically similar resistance patterns, the causative strains may differ in tenacity and linked resistances. The dominant (nosocomial) MRSA strains in the UK are the ST22/EMRSA-15 and ST30/EMRSA-16 lineages, which, aside from β-lactams, are resistant only to quinolones and macrolides. Other nosocomial clones, e.g., the Iberian type (ST247), are more broadly resistant [51]; nevertheless, the fitness of the UK strains may be greater (although this is difficult to prove). In any event, it is notable that EMRSA-16 has recently displaced the Iberian clone in the Canary Islands [52] (Fig. 3), that EMRSA-15 is rapidly spreading in the Czech Republic [53], and that an outbreak of EMRSA-16 proved to be exceptionally costly and difficult to eradicate in Sweden [54].

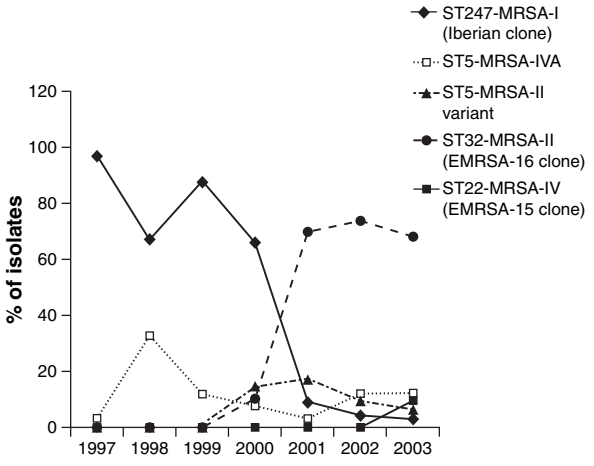

Fig. 3. Displacement of Iberian clone of MRSA (ST247-MRSA-I) by EMRSA-16 (ST32-MRSA-II) in Gran Canaria. Reproduced from Montesinos *et al*. [52] with permission.

E. coli strains with CTX-M ESBLs provide a further example of differences underlying apparent similarity, since they vary in clonality, enzyme type, and associated resistances. In the UK (and most of the rest of Europe), most producers have CTX-M-15 β-lactamase linked to OXA-1, with the latter conferring resistance to penicillin–β-lactamase inhibitor combinations [55]. In some regions, the producers are substantially clonal in their population structure; in others, they are diverse [56]. In Spain, the numerous producers largely have CTX-M-9 or CTX-M-14 enzymes [57], are non-clonal, and may be clinically susceptible to amoxycillin–clavulanate, even in bacteraemia [58].

Two further examples of important clonal differences among countries are, first, for pneumococci, and second, for *Clostridium difficile*. In the case of pneumococci, the prevalence of different serotypes varies with the country, affecting the potential coverage of the conjugate vaccine [59], which is directed against the seven serotypes that dominate and account for most penicillin resistance in North America. In the case of *C. difficile*, hyper-toxin-producing, fluoroquinolone-resistant ribotype 027 and 106 strains spread first in North America, where they were found to be associated with increased mortality. Subsequently, these have begun to spread in Europe [60,61].

CONCLUSION: THE IMPLICATIONS

Resistance varies with country, partly reflecting efforts concerning infection and prescribing controls, and partly reflecting chance factors such as whether a particular resistance clone has reached that location or not. Prescribing reflects underlying cultural attitudes and assumptions, which go deep into history.

The plethora of resistance surveys should be read with these caveats in mind, as well as with a careful consideration of potential sampling bias. National and international surveys aim primarily to show large-scale secular trends. If they are to be taken as benchmarks for reviewing resistance rates at individual hospitals, then great care should be taken to compare like with like. Nevertheless, if local resistance prevalence rates do appear to be radically different from national

data, it is legitimate to ask why, especially if the patient mix is comparable. Is it a reflection of infection control or antibiotic prescribing policies, microbiological sampling or testing policies, or does the difference reflect the local presence and dissemination of resistance types or strains that are not nationally prevalent? When we lecture internationally, we repeatedly hear questions such as: 'We have major problems with ceftazidime-resistant *Pseudomonas* (or another pathogen) in our ICU; do you think that's because we use a lot of cephalosporins?' The response is always to ask whether the *Pseudomonas* is clonal, implying an infection control problem, or diverse, reflecting endemicity or repeated selection. It is disturbing how rarely the answer is known.

Surveillance data usefully guide antibiotic policy, particularly for empirical treatment, but care must also be taken to consider the risk-factors for particular patients: have they had other recent rounds of antibiotics, or have they been hospitalised, making it more likely that they will be carrying resistant strains? This is critical, considering the relationship between resistance and mortality in severe infections [62].

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